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Continuously Stirred Tank Reactor for Pharmaceutical and Chemical Applications

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Abstract

In the fields of drug synthesis and fine chemicals, the traditional kettle-type reactor with a small heat exchange area and the microreactor which is easy to clog, are not suitable for the reaction with fast reaction speed, large heat release, and high solid content. However, the continuously stirred reactor has the advantages of high mass and heat transfer efficiency, high reaction safety, and not easy to be clogged, and therefore, has a great potential for application. This paper reviews the research progress of continuous agitation reactors in organic synthesis, drug crystallization, and biocatalysis, hoping to provide a reference for applications of continuous agitation reactors in the pharmaceutical and chemical fields.

Keywords
- continuous stirred tank reactor
- organic synthesis
- drug crystallization
- biocatalysis

Introduction

Currently, traditional kettle-type reactors, continuous flow tubular reactors, and continuously stirred reactors are commonly used reactor types in chemical production in pharmaceutical and chemical fields.[1–3] Traditional kettle-type reactors have the advantage of versatility and easy operation and are suitable for small-scale production and laboratory research; however, they can increase the reaction risk due to the low production efficiency and uncontrollability of the residence time.[4–6] Continuous tube reactors have the advantage of high production efficiency and can accurately control the residence time while sample in structure and easy to maintain. However, they are easily limited by material viscosity, solid content, reaction time, etc.; therefore, they are difficult to cope with the continuous and stable production of complex chemical reactions. Continuously stirred tank reactors (CSTRs) are reactors that combine the advantages of kettle-type reactors and continuous flow tubular reactors. The materials in these reactors are mixed evenly and reacted by stirring, which is more suitable for solid particles or high-viscosity materials involved in the reaction. CSTR can be adapted to many different types of chemical reactions in the pharmaceutical and chemical industries mainly due to the uninterrupted/continuous production run with high production efficiency.[7–9] CSTR can reduce the liquid holdup compared with the kettle-type reactors. Cherkasov and Nandiwale et al reviewed the application of CSTR in drug synthesis involving solids.[10,11] However, in this paper, we review the progress of CSTR in various aspects of organic synthesis, drug crystallization, and biocatalysis. The reactor can be used as a complement to traditional kettle-type reactors and continuous flow tubular reactors.

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Application of Continuously Stirred Tank Reactor in Organic Reactions

Applications in Electrophilic Substitution Reactions

Susanne et al have developed a set of small-scale CSTRs.[12] It has a sequence of reaction by using *N*-pivaloyl-protected 3,4-dichloro aniline **1** as a raw material. As shown in ►**Fig. 1A**, the *o*-lithium reaction and intramolecular cyclization occurred upon treatment with *n*-butyllithium to afford the benzoxazolyl lithium **2**, which was further applied to the synthesis of benzoxazole analogs by capture reaction with a series of electrophiles.

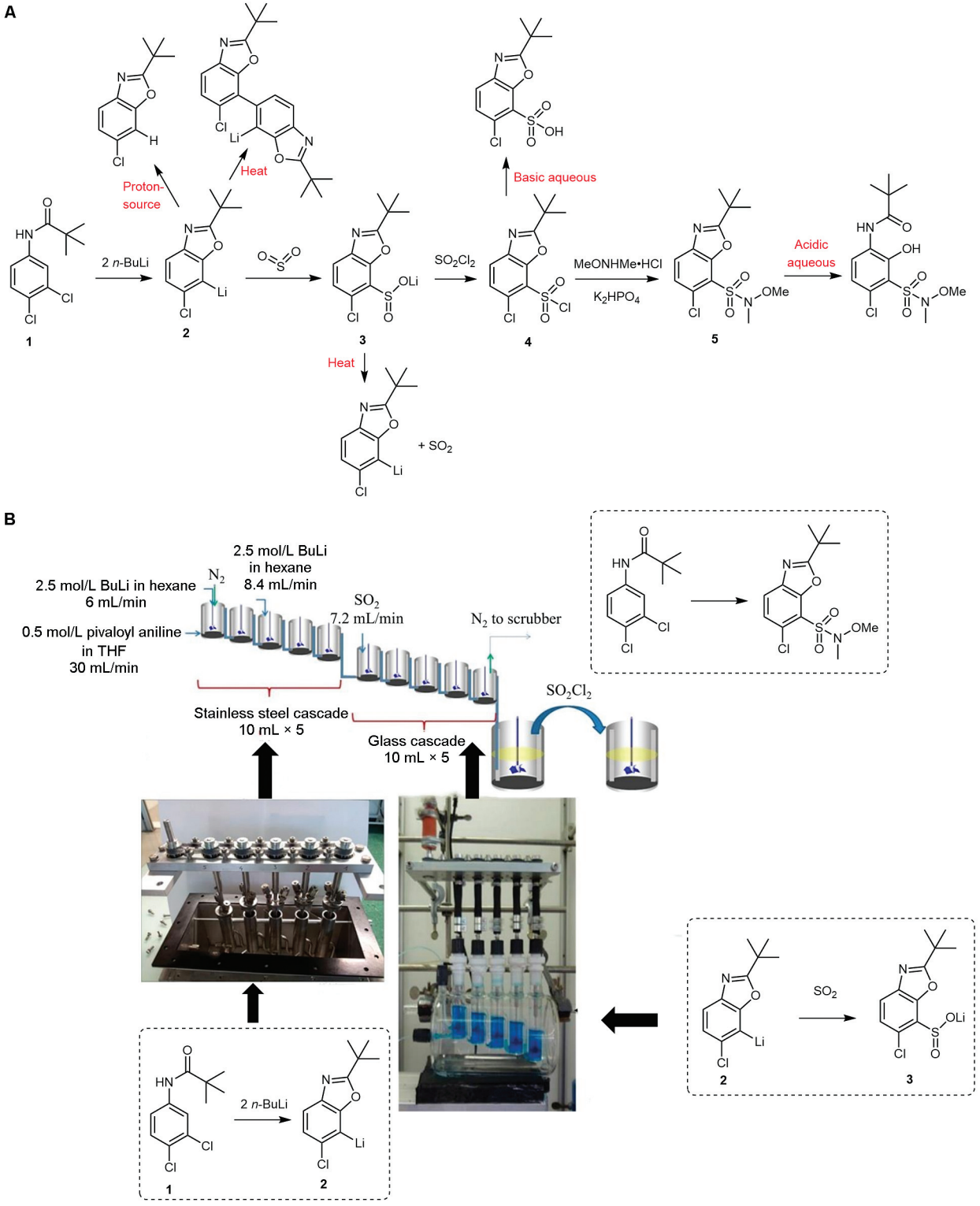

Fig. 1 (**A**) Synthesis process of benzoxazoles. (**B**) CSTRs for the *n*-butyllithium step and sulfur dioxide addition step. CSTR, continuously stirred tank reactor. Reproduced with permission from Susanne et al.[12]

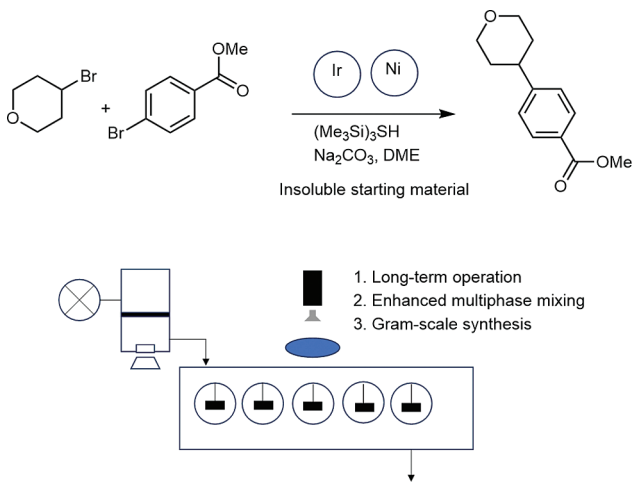

Fig. 2 Schematic of the reaction unit of a multiphase photocatalytic reaction using 4-bromotetrahydro-2*H*-pyran and methyl 4-bromobenzoate as raw materials.

The microchannel reactors are not suitable because of the formation of solids during the reaction process. However, the CSTR overcomes such shortcomings, i.e., it avoids the blockage of the reaction and improves the efficiency of the reaction. As shown in ►**Fig. 1B**, the CSTR unit employs 5 sets of 10 L stainless steel reactors in series as the first-stage reaction unit to carry out *n*-butyl lithium-mediated deprotonation and *o*-lithiation reactions. Then five sets of 10 L glass reactors are connected in series as the second reaction unit to prepare the lithium sulfate intermediate **3**. The average residence time of the reactor was 10 to 15 minutes with an overall yield of 65%, which was better than the 34% yield of the single kettle, and after 72 hours of continuous operation, the CSTR unit produced 17 kg of product with 99.8% purity.

Applications in Multiphase Photoredox Reaction

The continuous-stirring reactor has also been applied in multiphase photoredox reactions. For example, Pomberger et al described a CSTR multiphase photocatalytic reaction using 4-bromotetrahydro-2*H*-pyran and methyl 4-bromobenzoate as raw materials and a mixture of *N*,*N*-dimethylacetamide (DMA) and 1,2-dimethoxyethane as solvent.[13] The photo cross-coupling reaction was initiated by a 440-nm blue light-emitting diode in the presence of 2 mol% photocatalysts, 1 mol% nickel catalyst, tris(trimethylsilyl) silane, and Na_2CO_3 to produce methyl 4-(tetrahydro-2*H*-pyran-4-yl)benzoate. After 13 hours of continuous operation, the yield was 77%, and the conversion was complete.

As shown in ►**Fig. 2**, the unit consists of a slurry pump and a continuous CSTR. Na_2CO_3 was sent to the CSTR reactor in the form of a suspension in DMA by a slurry pump. The dissolved material was sent to CSTR by injection pump. This set of reaction equipment can be used to transport slurry material, occupying a small area. The device can run stably for 13 hours. This device solved the difficult problem of solids transport during the reaction process and realized the multiphase photocatalytic reaction in continuous flow chemistry.

Applications in Hydrogenation Reduction Reactions

Recently, Guan et al reported the improved hydrogenation reduction process in the synthetic routes of ezetimibe and (*R*)-eslicarbazepine acetate by combining continuous tubular technology and CSTR.[14] The target ezetimibe **8** was obtained by asymmetric hydrogenation and debenzylation reactions (►**Fig. 3**). The synthetic route consisted of three-phase reactions of solid, liquid, and gas. Since palladium carbon is a solid catalyst, CSTRs were used for the debenzylation reaction, and each reactor was fixed with Pd/C using a frit ferrule, and 9 reactors were filled with a total of 750 mg 10% Pd/C. The results

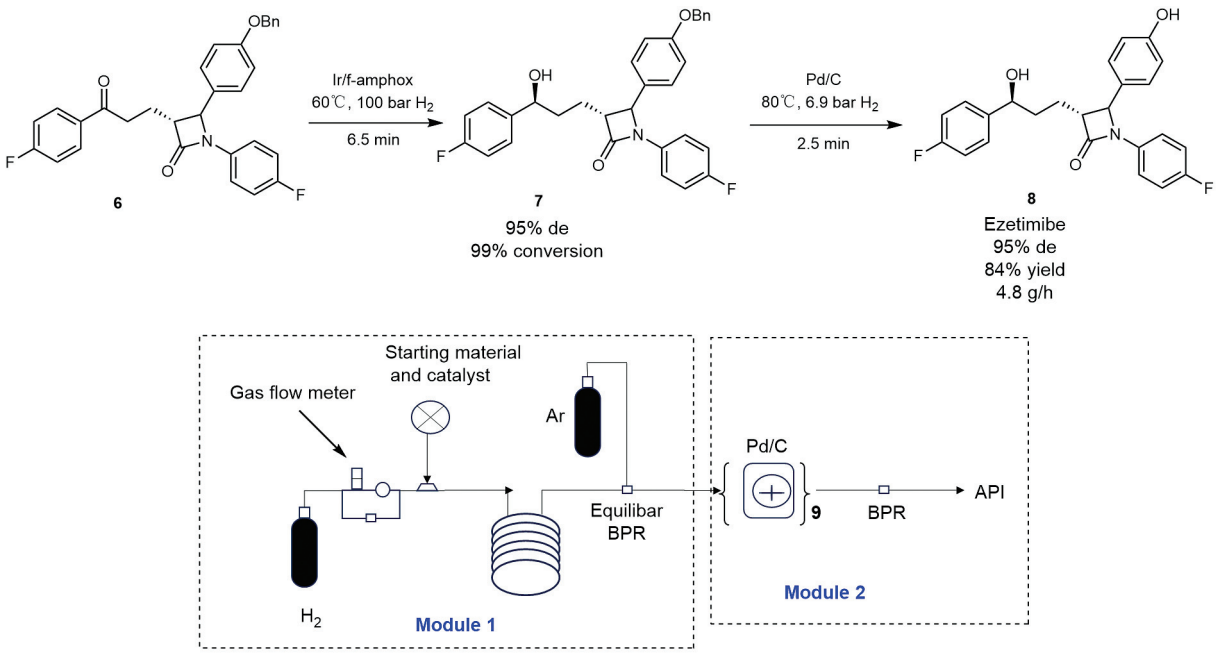

Fig. 3 The synthesis of ezetimibe and schematic for CSIRs for the debenzylation reaction. CSTR, continuously stirred tank reactor.

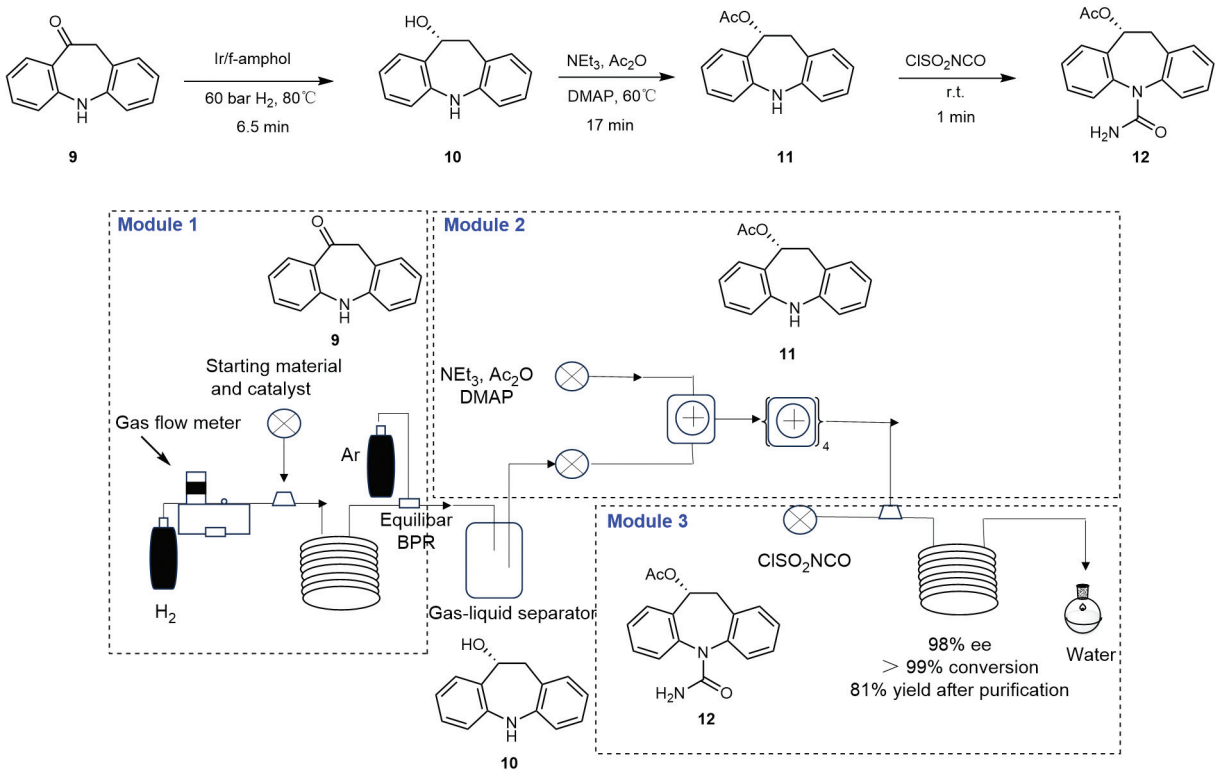

Fig. 4 The synthesis of (*R*)-eslicarbazepine acetate (**12**) and schematic for CSIRs for the hydrogenation (Module 1), acetylation (Module 2), and amination reactions (Module 3). CSTR, continuously stirred tank reactor.

showed that the continuous reaction of ezetimibe was achieved with a total residence time of 9 minutes, a production capacity of 4.8 g/h, enantiomeric excess (de) of 95%, and an isolated yield of 84%.

The asymmetric synthetic route of (*R*)-eslicarbazepine acetate **12** is shown in ►**Fig. 4**. The synthesis was performed, starting from the dibenzo[*b*,*f*]azepinone **9**, by tubular asymmetric hydrogenation, acetylation, and amination. The CSTR reaction was adopted for the hydrogenation reaction of compound **9** at 60 bar hydrogen and 80°C with a residence time of 6.5 minutes. The conversion rate was 98% and the enantiomeric excess (ee) of compound **10** was 98%. The product was collected in a gas–liquid separator and hydrogen was expelled through a tube filled with argon gas. Compound **10** was then mixed into 4 tandem CSTR at 60°C for acylation with a residence time of 17 minutes. The resulting dibenzo[*b*,*f*]azepin-10-yl acetate **11** was mixed with chlorosulfonyl isocyanate stream and passed through a 1-m tubular reactor to provide eslicarbazepine acetate **12**. The capacity of the unit was 1.6 g/h and the ee of the product was 98% with the separation yield being 81%.

Applications in Nucleophilic Substitution Reactions

Kopach and Braden et al have reported an example of the synthesis of ethoxetine intermediates by CSTR.[15,16] In this reaction, 4-chlorotetrahydro-2*H*-pyran **13** was used as raw material. In the presence of magnesium metal, the Grignard reagent **14** was formed, and the ethoxetine intermediate **16** was obtained by the nucleophilic substitution reaction with the amide **15** (►**Fig. 5A**).

When toluene is used as a solvent, side reactions tend to occur during the expected reaction. Therefore, a mixed system of 2-MeTHF/THF was selected through solvent screening, and in this system, the impurity content was <0.05%. The reaction unit consisted of three CSTR reaction units, in which reactor No. 1 and reactor No. 2 were used to generate the Grignard reagent and undergo nucleophilic substitution, and reactor No. 3 was used for quenching the reaction, as shown in ►**Fig. 5B**. The molar ratio of compound **13** and compound **15** was set to be 1:1.35, and solid magnesium was loaded into reactor No.1 every 15 hours, whereas the solvent 2-MeTHF/THF was continuously added to reactor 1. At 35°C, the conversion rate of reactor 1 reached 98%, and reaction 2 continued to react to increase the conversion rate.

To scale up the reaction, the capacity of each reactor was increased from 250 mL to 2 L for 80 hours of continuous operation, where magnesium was replenished every 4 hours in the first half of the reaction and every 8 hours in the second half, and the process was further improved. The automatic magnesium filling device in reactor No. 1 can operate normally during the production process. Since the solid magnesium forms magnesium pellets at the beginning of the reaction, no additional iodine and diisobutyl aluminium hydrogen are required to activate the new magnesium loaded into the reactor. The purity of CSTR products is greater than > 99%, with ee > 99% and the yield is 89%.

Recently, Mo and Jensen have developed a microtandem CSTR treatment for the mesylation reactions involving solid reactions.[17] The mesylation reaction of 2-octanol with methane sulfonyl chloride ($MeSO_2Cl$) is shown in ►**Fig. 6A**. The

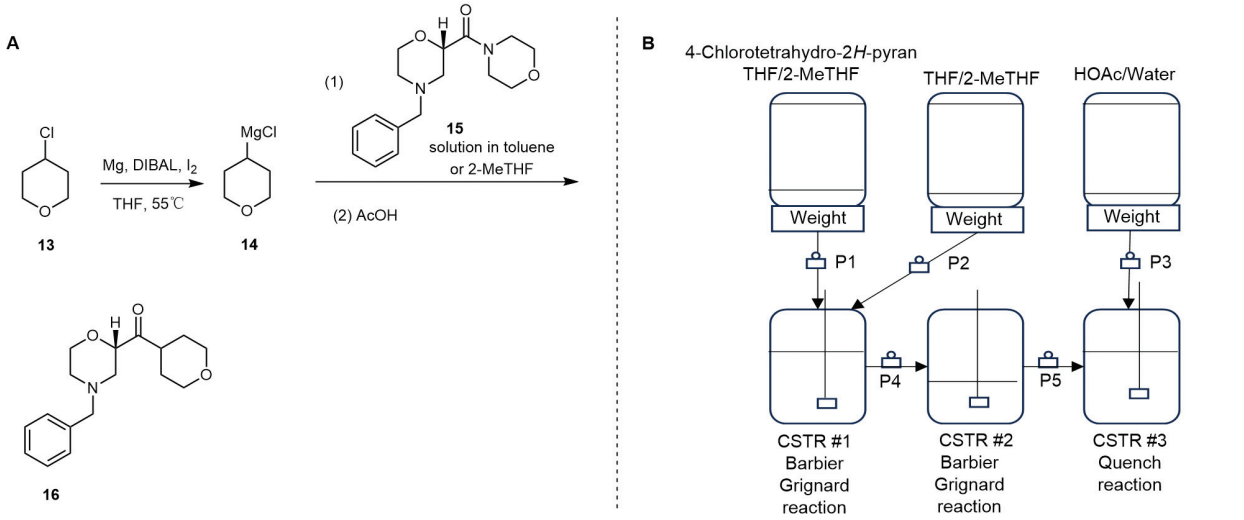

Fig. 5 (**A**) The synthesis of ethoxylate intermediates. (**B**) Process flow diagram. DIBAL, diisobutyl aluminium hydride.

reaction device is shown in ►**Fig. 6B**,**C**. In the micro-series CSTR system, each reactor had a cross-shaped magnetic stirring rod to suspend the solid particles, while stirring enhances the mixing and heat transfer effect in each chamber of the series CSTR. The residence time distribution (RTD) of the reactor was highly consistent with that of the ideal CSTR, so the mixing effect of the reactor was close to the ideal CSTR. As a result, the microseries CSTR reactor can process the feed liquid with solid content $\leq$ 4.4% and run continuously for 24 hours without plugging.

Browne et al used a flow reactor and mechanical agitation to form a milliliter series CSTR reactor,[18] in which the raw material morph was dissolved in methanol and configured as a solution with a concentration of 0.3 mol/L, and I_2 was dissolved in dichloromethane to prepare a solution with a concentration of 0.15 mol/L. The reaction is shown in ►**Fig. 7A**. The experimental device is shown in ►**Fig. 7B**. The peristaltic pumps were used to input the raw materials into the reactor, and a mechanical stirring slurry was added to each reactor for mixing so that the produced 4-iodomorpholin-4-ium iodide was completely suspended in the liquid. Due to the strong mechanical vibration, the *N*-iodomorpholinium hydroiodate runs stably in the reactor production process. Nine hours later, 208 g of product can be obtained, and the yield was 94%, which was higher than the traditional batch reactor.

Certainly, CSTR is not a perfect reactor and has some problems. Different CSTRs have different performances, such as heat transfer, reaction liquid mixing, and slurry handling

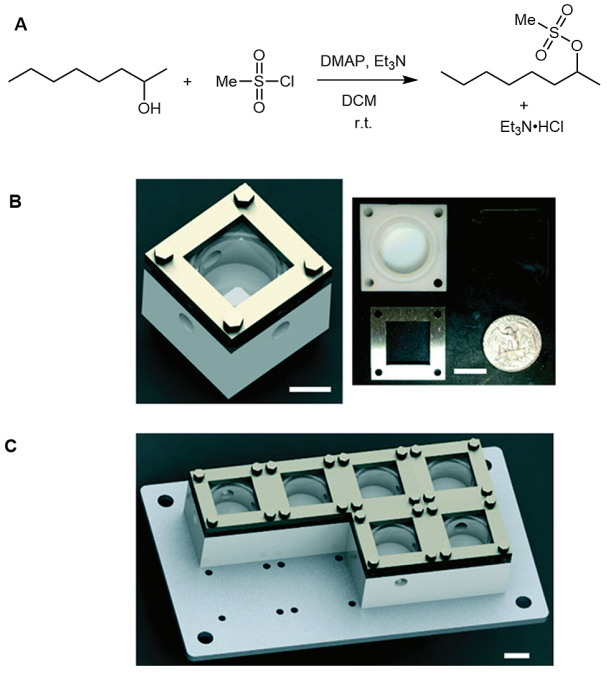

Fig. 6 Design of micro-series CSTR reactor. (**A**) The mesylation reaction of 2-octanol with methane sulfonyl chloride. (**B**) Single-stage CSTR design drawing. (**C**) Series CSTR design drawing. CSTR, continuously stirred tank reactor; DMAP, 4-dimethylaminopyridine.

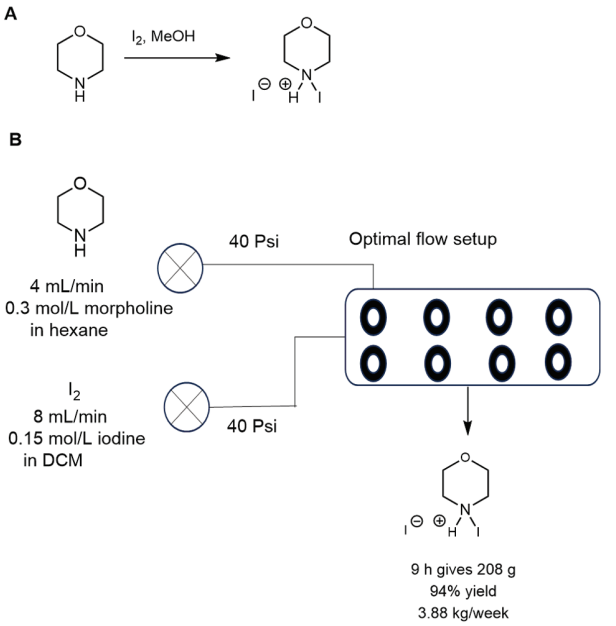

Fig. 7 (**A**) The synthesis of *N*-iodomorpholinium • HI. (**B**) Diagram of the experimental device.

ability. Also, CSTR has a wide RTD, which affects the selectivity, conversion rate, and yield. The ability to handle solids is often enhanced by ultrasonic vibration, intense mechanical agitation, and multiple CSTR reactors in series, which allows for better control of residence time. Therefore, when using CSTR, a proper compromise should be made between cost and process requirements.

Application of Continuously Stirred Tank Reactor in Drug Crystallization

Drug crystallization is one of the most important posttreatment operations in the pharmaceutical and chemical industries. Currently, most drug crystallization is carried out intermittently, and the crystallized substances may be different from batch to batch, resulting in variance and low crystallization yield. Therefore, it is becoming increasingly important to find a more efficient crystallization method. Compared with batch reactors, CSTR not only significantly reduces equipment costs, but also increases productivity by reducing residence time and auxiliary time.[19]

Currently, the most prolific continuous crystallization reactors are the mixed suspension, mixed product removal (MSMPR) crystallizer, and the continuous tube crystallizer, as shown in ►**Fig. 8**. The MSMPR crystallizer is suitable for reactions with a long residence time and slow crystallization process.[20] Continuous tube crystallizers are usually used for reactions with short residence times and high crystallization yields. Mechanical mixing methods inevitably cause wear and tear of the crystal particles, and therefore, a continuous tube crystallizer is preferred for a crystallization of large particles. However, for the MSMPR crystallizer, there are also some problems including a uniform mixing effect and poor control of the crystallization process in the MSMPR.

Du et al investigated the continuous crystallization process of cefminox sodium in an MSMPR crystallizer.[21] A laser kinetic method was used to assess the solubility of cefminox sodium in different solvents (►**Fig. 9A**). They suggested a similar solubility of cefminox sodium in ethanol and acetone, and for the drug use, they finally selected water and ethanol for crystallization.

A two-stage MSMPR continuous crystallizer was used for continuous crystallization of cefminox sodium (►**Fig. 9B**). A peristaltic pump was used to feed 18% cefminox sodium aqueous solution and the antisolvent ethanol into the crystallizer with mechanical stirring for crystallization at a volume ratio of 1:2, respectively. The optimum conditions were a total flow rate of 4.5 mL/min, a 1% crystal seed addition, a temperature of 288.15 K, and a crystallizer stirring rate of 250 r/min. The product, ceftizoxime sodium, was obtained by filtration and drying, and the average particle size of the crystals obtained by sequential crystallization was increased from 61.4 to 164 μm, and the yield was increased from 87.6 to 89.11%, as compared with that by conventional crystallization. When the MSMPR crystallizer was used, increasing the residence time increased the yield, but the purity was slightly reduced. Another method to increase the yield is mother liquor concentration, i.e., the mother liquor is filtered and concentrated and then fed into the next crystallizer.

Alvarez et al applied a multistage continuous MSMPR crystallizer for the crystallization of cyclosporine.[22] They recycled the mother liquor to improve the crystallization yield of cyclosporine, as shown in ►**Fig. 10**, where cyclosporine crystallized in 30% (w/w) cyclosporine acetone solution at 53°C. A peristaltic pump was used to input the cyclosporine solution into the first reactor, and the concentration of 20% (w/w) mother was input into the second reactor for further crystallization. The volume of each reactor was 30 mL, the total residence time was 500 minutes, and the temperatures of the first, second, and third reactors were 30, 14, and 14°C, respectively. As a result, the yield was increased from 74 to 87% compared with the conventional crystallization method.

In a study on the crystallization of cyclosporine, Li et al developed a multistage continuous cooling crystallization process by using an MSMPR crystallizer.[23] The experimental results are shown in ►**Table 1**. The theoretical yield and

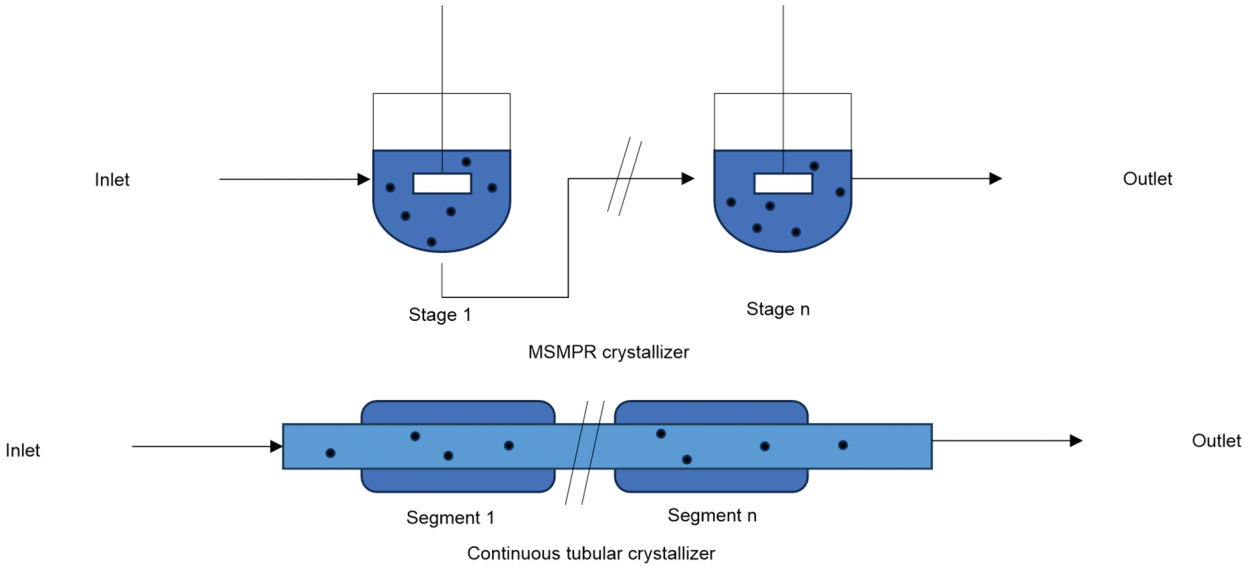

Fig. 8 Schematic diagrams of MSMPR crystallizer and tubular continuous crystallizes. MSMPR, the mixed suspension, mixed product removal.

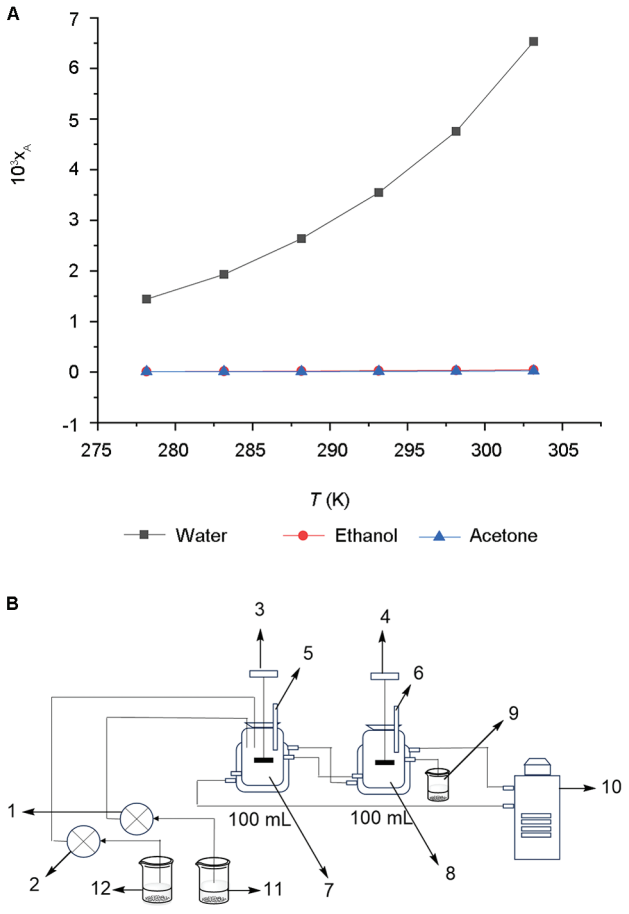

Fig. 9 (A) Solubility of cefminox sodium in different solvents. (B) Experimental setup for continuous crystallization of cefminox sodium. 1, 2, peristaltic pump; 3, 4, mechanical stirring; 5, 6, thermometer; 7, 8, crystallizer; 9, product; 10, super thermostatic bath; 11, ethanol reaction solution; 12, cefminox sodium aqueous reaction solution.

purity calculated by the solubility of batch crystallization are 86.0 and 97.0%, respectively. The results of the continuous crystallization of cyclosporine show that the optimum yield and purity can be achieved by changing the number of reactors, residence time, and temperature. The total residence time of grade 1 to 3 MSMPR crystallization is 9, 18, and 15 hours, respectively. The yield of grade 3 MSMPR crystallized for 18 hours is similar to that of grade 5 MSMPR crystallized for 15 hours, but the crystal purity of grade 3 MSMPR crystallization (98.0%) is slightly better than that

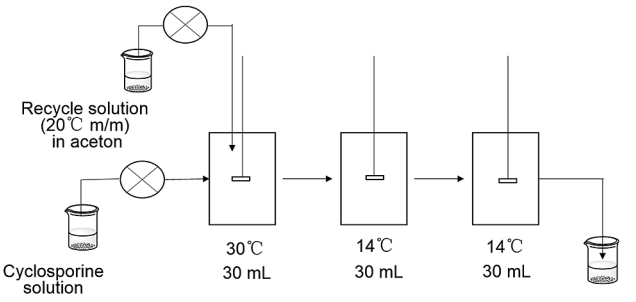

Fig. 10 Schematic diagram of the MSMPR crystallizer for the crystallization of cyclosporine, in which the mother liquor was recycled. MSMPR, the mixed suspension, mixed product removal.

of grade 5 MSMPR crystallization (97.3%). Compared with the initial 3-stage MSMPR crystallization, the optimized results can increase the crystal purity by about 5% and the yield by about 10%.

Currently, there are three types of continuous tubular crystallizes: the plunger flow crystallizer (PFC), the segmented flow crystallizer (SFC), and the oscillating flow crystallizer (OFBC), as shown in ►**Fig. 11**.[24] PFC is characterized by narrow microchannels and low flow rate and has been used for the crystallization of small molecules, but not for continuous crystallization of protein drugs due to the fact that biomacromolecules like protein tend to accumulate.[25–27] SFC is characterized by a segmented flow, in which a string of bubbles separates the continuous flow pattern of the crystallizing solution. Each liquid segment is similar to a miniature batch crystallizer, with gas and liquid flowing through the tube at the same time, reducing the possibility of crystal precipitation and clogging the tubes.[28,29] It is also possible to use an immiscible liquid in place of gas to form a segmented plug flow, which can be passed downstream to carry out a liquid-phase separation operation. OFBC is based on a tubular reactor that generates vortex circulation through radial motion and radial uniform mixing based on the baffle region.[30] The uniform rate of crystal nucleation makes OFBC superior to PFC in terms of crystallization performance, and it is widely used for the continuous crystallization of small molecule drugs.[31]

In 2016, Cole et al reported the continuous crystallization of merestinib intermediate **19**.[32] The reaction is shown in ►**Fig. 12A**. During the synthesis process, there were some organic impurities (►**Fig. 12B**), as well as some inorganic salts

Table 1 Effect of the stages, temperature, and residence time on yield, purity, and average crystal size of the continuous crystallization of cyclosporine

	Total residence time (h)	Yield (%)	Crystal purity (%)	Mean crystal size, $L_{4,3}$ (μm)
Batch at equilibrium	–	86.0	97.0 ± 0.2	–
1-stage MSMPR crystallization	9	76.3 ± 0.7	97.4 ± 0.1	83.9
3-stage MSMPR crystallization	18	80.4 ± 0.3	98.0 ± 0.3	88.2
5-stage MSMPR crystallization	15	80.8 ± 0.3	97.3 ± 0.2	96.1

Abbreviation: MSMPR, the mixed suspension, mixed product removal.
Source: Reproduced with permission from Li et al.[23]

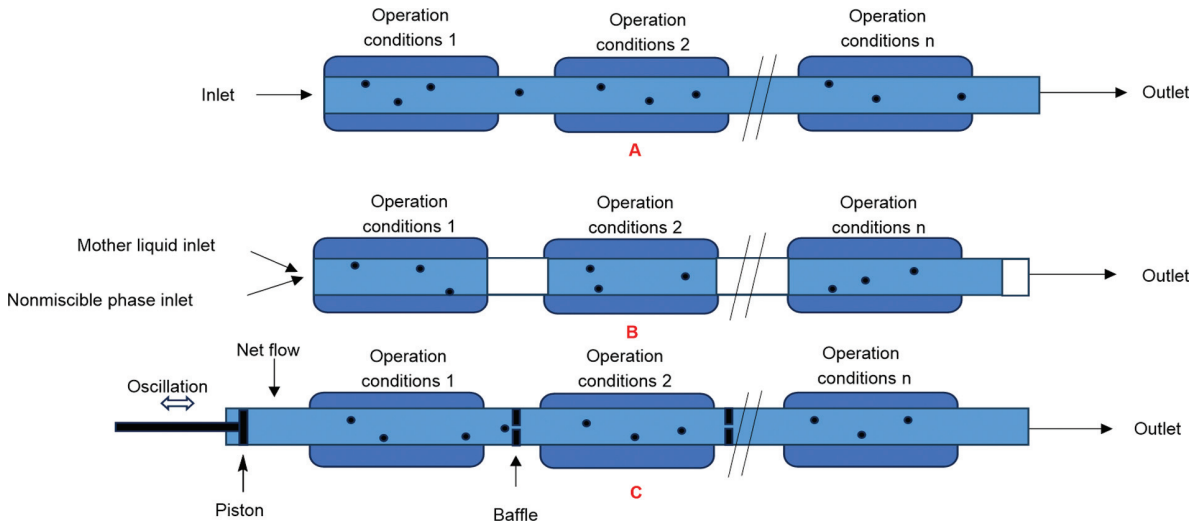

Fig. 11 Continuous flow tubular reactor. A, plunger flow crystallizer; B, segmented flow crystallizer; C, oscillating flow crystallizer.

and Pd, etc. In this work, a continuous crystallization was carried out using $V_{ethanol}/V_{water} = 1{:}1$ to avoid liquid–liquid phase distribution, which is cost-effective and environmentally friendly (►**Fig. 12C**). The crystallizer was a Mettler–Toledo reactor with automated operation. The volume of a single CSTR was 5 L. Crystallization reached a steady state after 8 hours of operation. TZ 1 was to transfer the slurry from MSMPR 1 to MSMPR 2, and TZ 2 was to transfer the slurry from

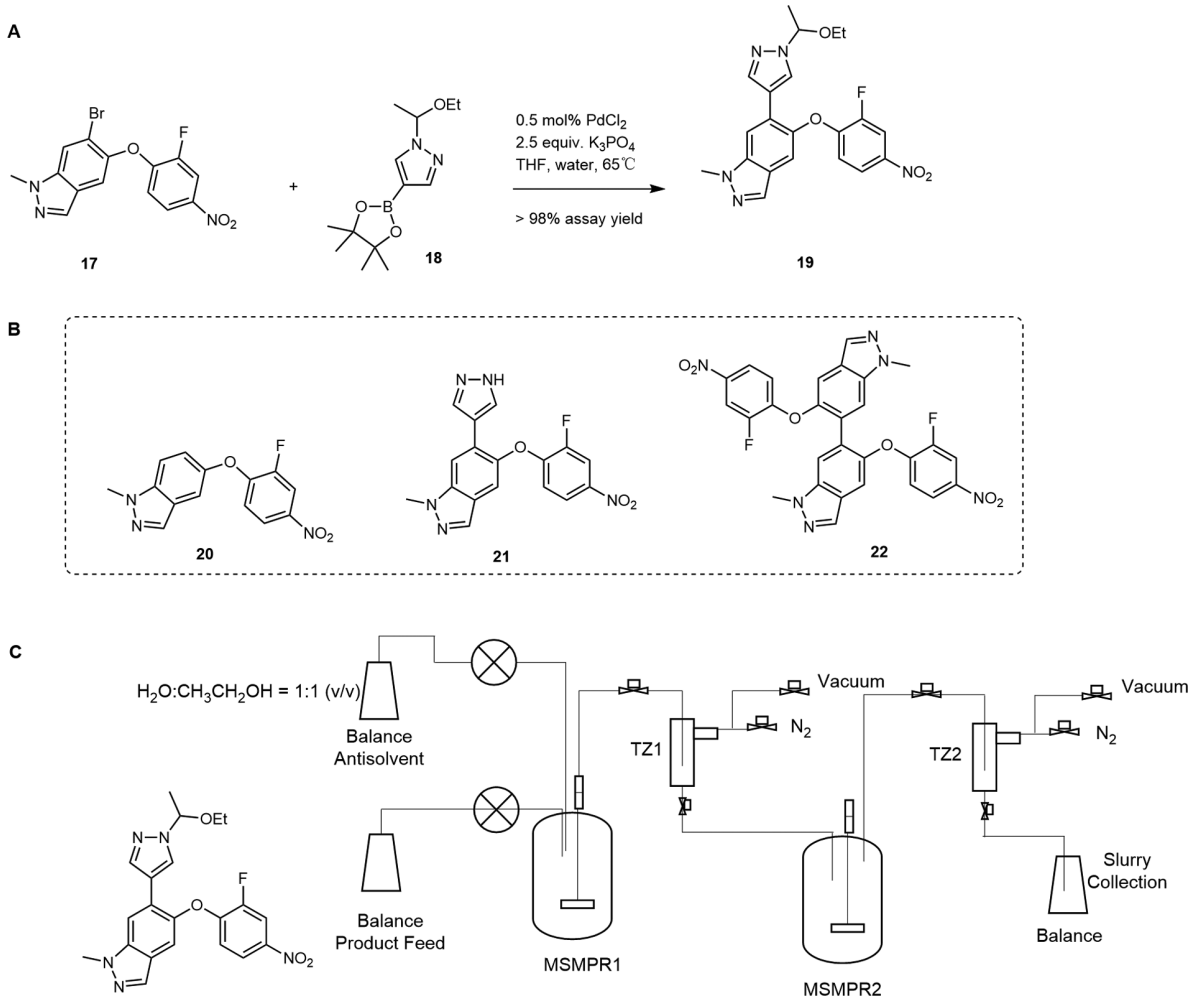

Fig. 12 (**A**) Synthesis of merestinib intermediates. (**B**) Organic impurities present in the synthesis of merestinib intermediates. (**C**) Continuous crystallization of merestinib.

MSMPR 2 to the vessel (►**Fig. 12C**). Continuous crystallization was carried out by recrystallizing the 1,100 g intermediate **19** at 21°C, 100 hours later, 902 g of pure product was obtained. The crystallization yield was 82%, the product purity was 98.99 to 99.30%, and the Pd content was reduced from 51 ppm in solution to less than 5 ppm in solid.

Application of Continuously Stirred Tank Reactor in Biocatalysis

Chemical reactions and multistage enzymes can be efficiently used for the synthesis of pharmaceutical intermediates through the coupling continuous flow technology.[33–40] Recently, Lindeque et al combined glucose oxidase with catalase to oxidize glucose to gluconic acid in a CSTR (►**Fig. 13A**).[41] In a conventional batch reactor, high pressure of 25 bar is required to increase the solubility of oxygen in the solution to complete the biocatalytic reaction, and the oxidation reaction is a hazardous process.

CSTR is proven to be effective in increasing the mass transfer interfacial area and volumetric mass transfer coefficient (kLa) in gas–liquid systems under atmospheric conditions. The use of a two-stage CSTR in series (►**Fig. 13B**) increased the total conversion by a factor of 3. The yield was 95 g_{GA}/g_{GOx} (1 g of enzyme-catalyzed to produce 95 g of gluconic acid), which was 1.7 times better than the yield of a single reactor. Two streams of material are pumped into the reactor at the same flow rate at atmospheric pressure. Catalase converts the hydrogen peroxide generated by the reaction into water and oxygen, avoiding the inactivation of glucose oxidase. Therefore, CSTR solves the safety problem of oxygen participation in the reaction in biocatalysis and has a high conversion rate.

Meanwhile, Bak et al employed a spontaneous phase separation membrane (μ-CSTR) to biocatalyse methane phase transfer to methanol at ambient temperature and pressure (►**Fig. 14**).[42] Methanotrophic bacteria were used as the catalysis, and the catalytic mechanism including methane monooxygenase and inactivated methanol dehydrogenase, is shown in ►**Fig. 14B**. The experimental setup is shown in ►**Fig. 14A**. μ-CSTR consists of a biocatalytic reaction inner chamber, a membrane separation, and an oil–water phase continuous extraction unit. In which methane-oxidizing bacteria inside the reactor convert methane to methanol and retain the strain through membrane separation. The products enter the oil (dodecane and fluorinated oil (FC40)) and aqueous phase extraction region outside the membrane, and the products are obtained by separating in a continuous extraction device. Under the optimal process conditions, the yield of 1.5 g DCW/L strain concentration (DCW is the total biomass obtained by centrifugal collection of a unit volume of microbial culture solution, repeated washing of bacteria with water, and accurately weighing the bacteria after frequent pressure or vacuum drying) was about 4.0 g/L for 24 hours of continuous operation, which was 15 times better than that of the intermittent reaction (0.26 g/L). The average methanol yield was 0.265 ± 0.015 g/L/h, and the highest yield was 0.304 g/L/h, which was superior to that of the intermittent reaction (0.003–0.005 g/L/h).

For the preparation of flavor-active acetate esters, Perdomo et al used mycelium-bound lipase to catalyze the sequential preparation of acetate from isoamyl alcohol and acetic acid.[43] The reaction is shown in ►**Fig. 15A**, which indicates that the enzyme has a high stability to both substrate and product. The reactor volume in the experimental setup was 200 mL, the suspension was stirred with a

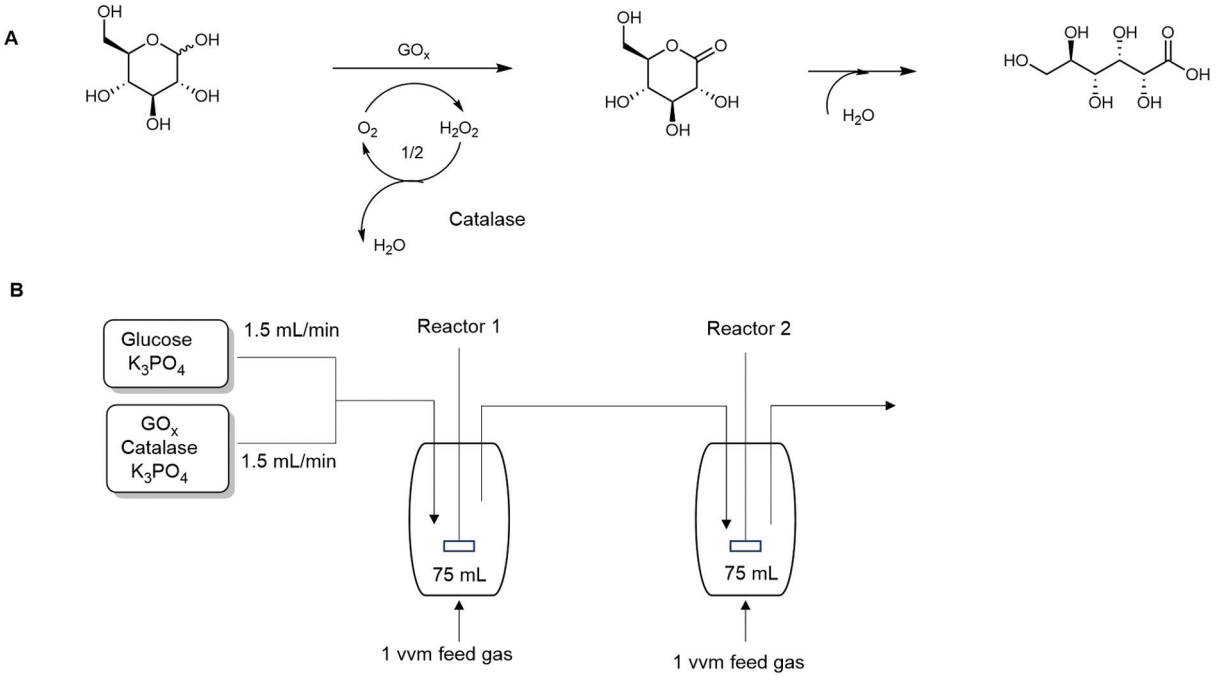

Fig. 13 (**A**) Glucose oxidation. (**B**) Reactor configuration with two identical CSTRs in series. CSTRs, continuously stirred tank reactors.

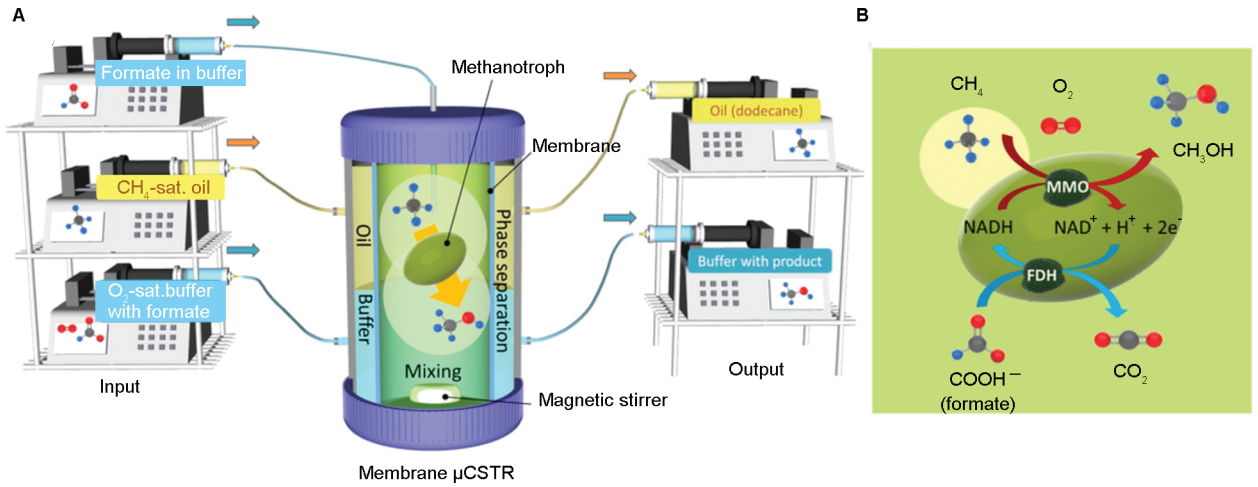

Fig. 14 (A) Bak et al' separation membrane μ-CSTR unit diagram. (B) Schematic of methane–methanol conversion. MDH, inactivated methanol dehydrogenase; MMO, methane monooxygenase. (Reproduced with permission from Bak et al.[42])

magnetic stirrer and the material was fed using a peristaltic pump in ►**Fig. 15B**.

A mixed solution of acetic acid and isopentyl alcohol and 25 g/L of *n*-heptane solution of mycelium-bound lipase was formed. A total flow rate of 0.1 mL/min and a residence time of 500 minutes at 50°C resulted in a conversion of 82%, a reaction rate of 0.092 μmol/min, and an overall yield of 169 mg/mL (amount of ester formed per volume of the reactor). This rate was slightly better than 0.089 μmol/min of a batch reactor, indicating a good mixing of the reaction solution in the CSTR. After 16 hours of operation, 98% conversion was achieved and the CSTR was run for 10 days without any deactivation of the biocatalyst activity. In conclusion, the combination of mycelium and lipase can realize an efficient continuous production of acetate.

Lipases produced by solid-state fermentation have also been used by Martínez-Ruiz et al as biocatalysts for continuous synthesis of ethyl oleate in a CSTR.[44] The reaction is shown in ►**Fig. 16A**. The experimental setup is shown in ►**Fig. 16B**. The lipase prepared by solid-state fermentation was dried to a water content (<1% w/w), thereby preserving its structure and catalytic activity. The reaction was carried out in a reactor of 1 L volume, with *n*-hexane as a solvent, oleic acid, and anhydrous ethanol as feedstock, an oleic acid concentration of 50 mmol/L, a molar ratio of oleic acid/ethanol of 1:2, a flow rate of 2 mL/min, and a stirring rate of 300 rpm. As a result, the substrate conversions were maintained at a constant rate of between 78 and 82% during the 23 hours of continuous operation.

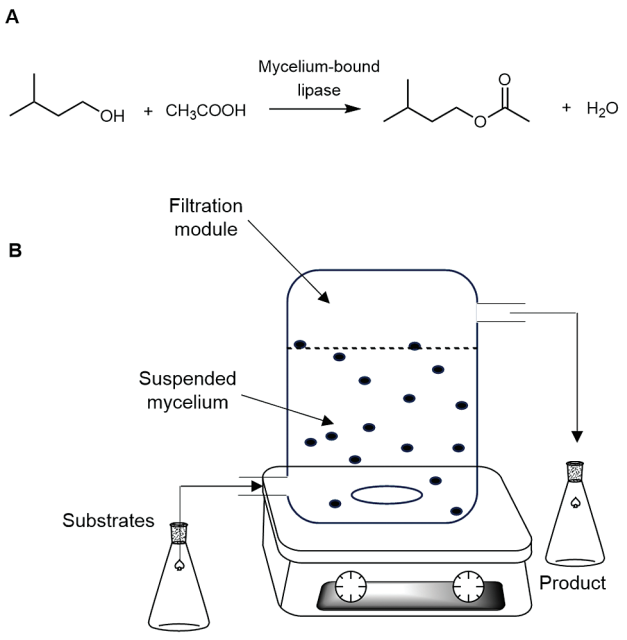

Fig. 15 (A) The reaction of isopentanol with acetic acid. (B) CSTR device diagram. CSTR, continuously stirred tank reactor.

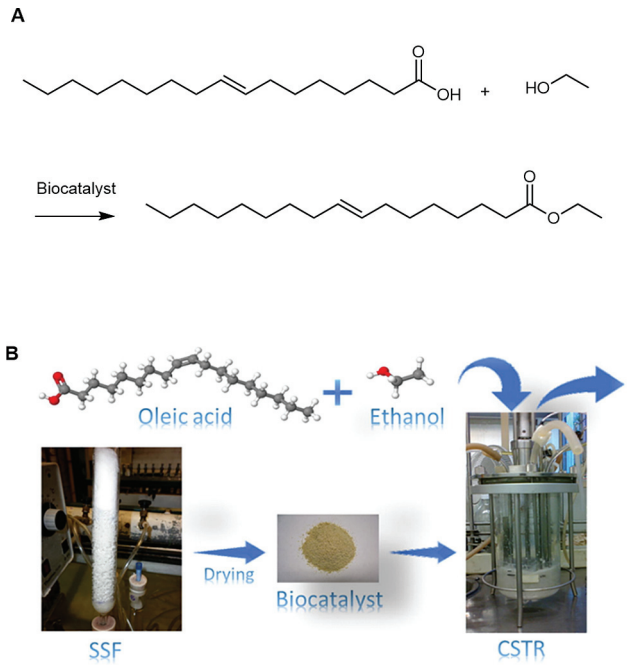

Fig. 16 (A) The reaction between ethanol and oleic acid. (B) Diagram of the experimental set-up.

Conclusion

CSTR and tandem continuous stirred kettle reactors are well-established technologies in the field of organic synthesis. CSTR can handle feedstocks with high solids content and has been widely used in continuous crystallization, which greatly reduces the cost, and enables applications in continuous biocatalysis. CSTR has been one of the main reactors for converting batch production into continuous production and realizing the benefits. However, compared with the continuous tubular reactor, CSTR has mechanical mixing capabilities, especially for multiphase systems, which can significantly improve mass and heat transfer, and therefore one of the key reactors to realize greener, safer, and more efficient production of chemical products.

Conflict of Interest
None declared.

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